

OBESITY: CLINICAL AND BIOLOGICAL PERSPECTIVES

12/05/02

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OUTLINE

- 1. Epidemiology of obesity. Recognition of the substantial increase in the prevalence of obesity in the US population in the past few decades. It is currently estimated that at least 22% of adults are clinically obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) and more than 50% are overweight ($\text{BMI} \geq 25$). Brief description of the public health consequences and societal costs of obesity.**
- 2. The obese individual: clinical and psychosocial consequences that are secondary to the obese state. Most co-morbidities vary directly in degree or intensity with increases in BMI. Reversibility of many co-morbidities with weight reduction.**
 - Hypertension**
 - Coronary artery disease**
 - CVA**
 - Hyperlipidemia**
 - Type 2 diabetes mellitus**
 - Insulin resistance**
 - Cholelithiasis**
 - Gout**
 - Osteoarthritis**
 - Sleep apnea, hypoventilation**
 - Menstrual abnormalities**
 - Hyperandrogenism, hirsutism**
 - Polycystic ovaries**
 - Malignancies: breast, endometrium, colon, other**
 - PSYCHOSOCIAL HARM**

Known etiologies of human obesity:

a) **Acquired:** (drugs, endocrinopathies, CNS lesions):

1) **Drugs:** insulin, sulfonylureas, glucocorticoids, psychotropic agents.

2) **Endocrinopathies:** hypothyroidism (rarely associated with significant increases in body fat), Cushing's syndrome, insulinoma.

3) **Brain lesions** (e.g., craniopharyngioma)

b) **Genetic syndromes:** rare; often associated with other abnormalities.

Examples: Prader-Willi (loss of paternal 15q11-13)

Alstrom (linked to 2q12-13)

Bardet-Biedl (?11q13)

Lep -, LepR -, POMC, MC-4R, PC-1, PPAR α , β_3 AR, others.

c) **Idiopathic** (>95%). There is substantial heterogeneity within this group, and it is likely that a proportion of obese individuals will be found to be affected by specific etiologies.

4. Definition of obesity: Obesity is marked by an increase in the amount of potential energy that is stored as adipose tissue triglyceride.

SOURCES OF ENERGY IN A 70 KG HUMAN

- **CHO** (500-600 kcal from 30 gm free glucose in ECS + 150 gm glycogen in liver)
- **PROTEIN** (approx. 20,000 kcal in amino acids derived from skeletal muscle protein)
- **FAT** (approx. 150,000 kcal stored as adipose tissue triglyceride). Highly differentiated function of adipocytes allows most of the stored energy to reside in a small subset of cells in the body.

NORMAL: of the order of 15×10^9 adipocytes containing 0.7 mgm lipid/cell = approx. 10-15 kg triglyceride (= approx. 10^5 kcal).

OBESE: increase in fat cell size and number; e.g., 100×10^9 adipocytes containing 1 mgm lipid/cell = 100 kg triglyceride = 7.9×10^5 kcal.

Weight loss involves shrinkage of adipocyte size as each molecule of triglyceride is hydrolyzed into 3 free fatty acid molecules plus one molecule of glycerol. However, weight loss is not accompanied by reduction in fat cell number.

Normal fat storage is sufficient for at least one month of fasting, often more. Obese individuals carry sufficient triglyceride to sustain months of caloric deprivation. Nonetheless, the bio-behavioral regulatory system sounds an “alarm” (hunger, decreased metabolic rate) when the fuel level falls by only a few % of max. Body weight is defended, despite medical and social consequences. This tight control of body weight may have conferred evolutionary advantages. Substantial research efforts are currently aimed at elucidating the mechanisms of body weight regulation.

5. In nearly all instances of human obesity, there is no established lesion or pathophysiology. Body weight distribution is a continuous variable in the population, and the definition of obesity is arbitrary.

Attempts to establish an “etiology” have concentrated on energy metabolism and feeding behavior. Numerous studies have demonstrated that, at steady state, obese subjects consume (and metabolize) a large number of calories daily, generally more than lean individuals. Further examination of population-based data discloses that the energy requirements of most obese subjects can largely be predicted on the basis of lean body mass, as is true of normal-weight and lean individuals. There is no evidence to suggest that obese subjects are hypometabolic when in the obese state.

Some studies have shown that the metabolic rates of weight-stable reduced-obese individuals are lower than predicted. In addition, some studies have reported other alterations in behavior and endocrine/metabolic function in reduced-obese individuals. These include chronic hunger, persistence of a great number of small adipocytes, reduced T3 levels, bradycardia, cold intolerance, hypercarotenemia, low catecholamine levels, suppressed hypothalamic-pituitary-adrenal responses, and inevitable weight regain.

As discussed in the lecture, there is little evidence that obesity is a feeding disorder or a disorder of energy metabolism, other than the storage of excessive calories as adipose tissue triglyceride. There is certainly no evidence that obesity has a psychiatric or behavioral etiology.

6. Treatment: There is no known permanent treatment for obesity. In the absence of identification of a specific pathophysiology, we can effect only modest degrees of weight reduction in most instances. Even patients who have lost considerable amounts of weight are at risk of weight regain within months. Current treatment regimens include:

- a) diet and exercise---these form the cornerstone for every treatment regimen
- b) behavior modification
- c) anti-obesity medications: amphetamine-like drugs carry potential for habituation and have, at best, short-term efficacy. Two recently-approved drugs are sibutramine (a central NE and serotonin re-uptake

inhibitor) and orlistat (an intestinal lipase inhibitor). Weight loss is generally of a modest degree, only in a subset of patients, and maintained only when on therapy. About 90% of individuals regain lost weight within 6 months; 95% within 2-3 years.

- d) gastric surgery (limited to morbidly obese patients)
- e) prevention of obesity in the pediatric population

It is important to distinguish the likely risks and benefits of drugs used to treat specific etiologies (e.g., recombinant leptin for homozygous *lep^o* obese patients) from those associated with drugs used on the general obese population (e.g., current FDA-approved drugs). If specific etiologies can be identified, it is likely that more effective drugs will be developed. Lacking this, new drugs will most likely attempt to target normal control mechanisms. This approach will have to contend with the redundancy of the weight-regulating system. In addition, adverse side effects of many new drugs may limit development. Future research will determine whether this approach will be fruitful. Rigorous development programs, including well-controlled clinical trials, are required to produce safe and effective new drugs.

Current FDA guidelines for obesity drug development include demonstration of long-term efficacy (at least one year) in a randomized, double-blind, placebo-controlled, parallel-group study. Patients must lose at least 10% of initial body weight (or about 5% of body fat) to demonstrate reduction in co-morbidities (blood pressure, lipids, blood glucose). Therefore, efficacy is aimed at achieving at least this degree of (placebo-subtracted) weight loss in the course of 6-12 months of treatment. Adverse events are closely monitored and compared to those in the placebo group. Body composition is monitored (e.g., by DEXA scanning) to ensure that weight reduction entails loss of fat and not excessive diminution of lean body mass.

7. Leptin is an adipocyte-derived polypeptide hormone with m.w. @ 16.5 kD. This newly-discovered hormone plays an important role in weight regulation. Recent experience with recombinant leptin in treatment of rare patients with leptin deficiency provides an important lesson in therapeutics.

Leptin is secreted from fat cells into the blood and binds to specific neuronal receptors in the hypothalamus. Leptin regulates body weight by decreasing appetite and increasing the metabolism of adipose tissue triglyceride. In rodents, absence of leptin (e.g., the *ob/ob* mouse) or of functional leptin receptors (e.g., the *db/db* mouse or the *fa/fa* rat) leads to a syndrome of extreme obesity. In humans (and normal animals), leptin production increases with increases in fat mass. In humans, plasma leptin levels strongly correlate with body fat. Leptin levels are higher in women than in men, perhaps owing to gender-related differences in the anatomic distribution of body fat.

Leptin is transported into the brain, in part via receptors in the choroid plexus. In the brain, leptin binds to other receptors in the hypothalamus and interacts with other elements related to control of feeding behavior and energy expenditure (including neuropeptide Y, POMC, and other neuropeptide and monoamine systems). Obese humans generally have an increase in plasma leptin concentrations. Despite this, obese subjects have difficulty suppressing appetite and increasing energy expenditure. This has suggested to some investigators that obesity is associated with leptin resistance. The nature of this resistance has not been elucidated. Levels of endogenous leptin decline with food restriction and weight loss in humans and experimental animals. This led to the hypothesis that injections of recombinant human leptin might be useful in the treatment of human obesity. Although injections of leptin (either peripherally or into the cerebral ventricles) cause weight loss in rats, subcutaneous injections of leptin were found to have little effect in obese humans. To date, clinical trials have demonstrated that subcutaneous r-metHu-leptin has only a modest effect in inducing weight loss in some obese subjects.

In contrast, recombinant leptin has been successful in treating an extremely obese patient with a homozygous frame shift mutation in the leptin gene. This nine-year-old girl with no immunoreactive leptin protein in her blood (as a result of the mutation) exhibited hyperphagia with massive weight gain beginning at four months of age. By nine years, she weighed 92 kg. The patient was treated with low doses of recombinant human leptin, given subcutaneously. The dose was designed to achieve about 10 % of her predicted blood leptin concentration. The result of this treatment was loss of about 15 kg within one year. The weight reduction consisted entirely of fat loss, with preservation of lean body mass. There were no side effects of leptin treatment.

Thus a specific pathophysiology may be amenable to specific treatment that is safe and highly effective.

Further description of obesity drug development prospects will be presented.

The views presented in this outline and lecture are those of the lecturer and do not necessarily represent those of the FDA or the federal government.